# Delta opioid receptor regulation of ASIC1a-dependent neurotoxicity

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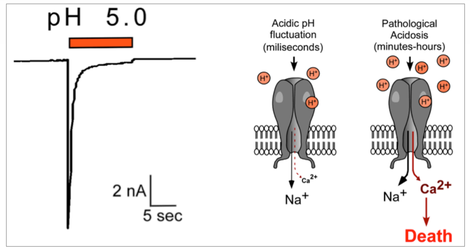
## Background

- Extracellular pH fluctuates in normal brain function and in disease, like ischemic stroke, multiple sclerosis, and traumatic injury.
- Acid-sensing ion channel 1a (ASIC1a) promotes neuronal death in pathologic acidosis.
- However, ASIC1 knock-out mice show abnormal drug seeking behavior and deficits in fear learning.

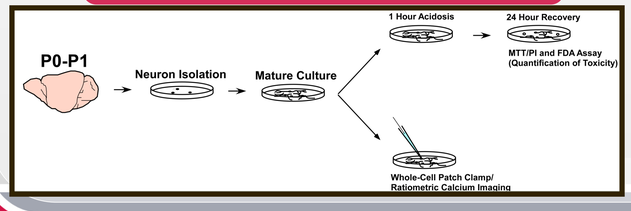



- Little is known regarding whether ASICs can be regulated by signaling pathways.
- Activation of the delta-opioid receptor (DOR) is neuroprotective in mouse models of ischemic injury.

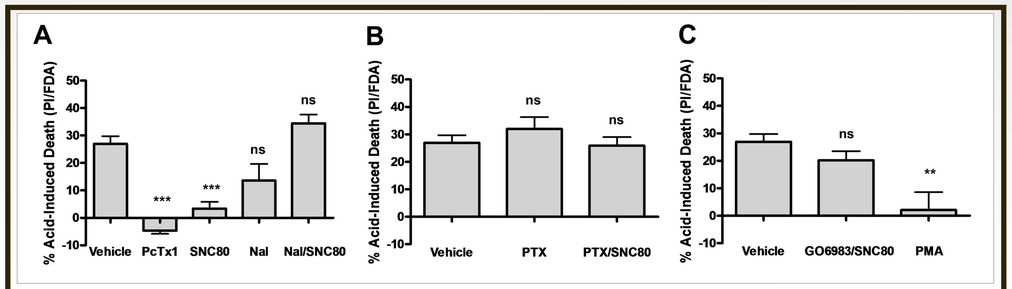
## Hypothesis

- **Therefore, we hypothesized that delta-opioid receptor agonists limit ASIC1a neurotoxicity through a unique mechanism.**
- DOR activation attenuates ASIC1a-induced neuronal death.
- However, DOR agonists do not affect ASIC currents or proton affinity.

## Methods




## 1. DOR agonists reduce ASIC1a dependent acidotoxicity in neurons



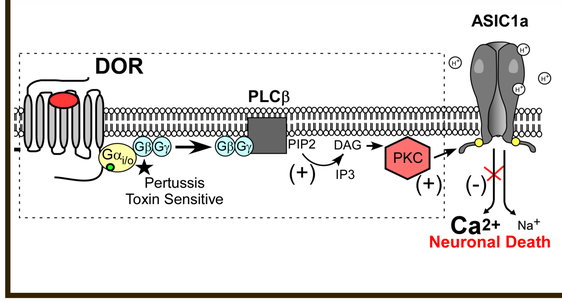




**Figure 1. DOR activation prevents acid-induced neuronal death in cultured mouse neurons in a Gαi/Gαo and PKC dependent manner. (A)** The specific ASIC1a inhibitor PcTx1 and DOR agonist SNC80 decreased acid-induced death ($p<0.001$). DOR inhibition by naloxone abolished neuroprotection. **(B)** Gαi/Gαo inhibitor PTX prevented protection afforded by SNC80. **(C)** PKC inhibitor GO6983 abolished protection and PKC activator PMA prevented acid-induced death ($P<0.01$). Summary of pathway outlined to left. Experiments conducted in presence of CNQX, MK801, TTX, and nimodipine.

## 2. ASIC electrophysiology is unaffected by DOR agonists

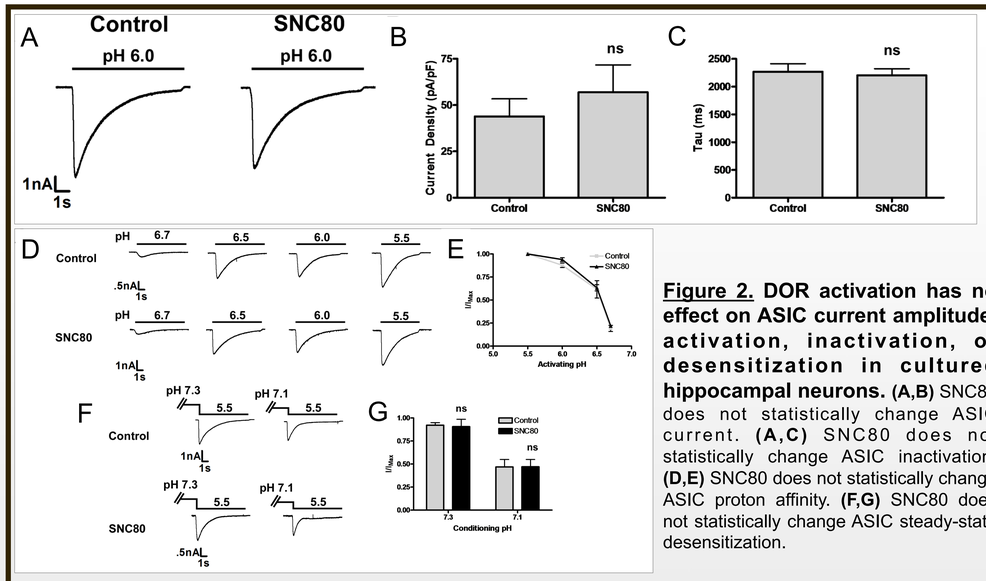



**Figure 2. DOR activation has no effect on ASIC current amplitude, activation, inactivation, or desensitization in cultured hippocampal neurons. (A,B)** SNC80 does not statistically change ASIC current. **(A,C)** SNC80 does not statistically change ASIC inactivation. **(D,E)** SNC80 does not statistically change ASIC proton affinity. **(F,G)** SNC80 does not statistically change ASIC steady-state desensitization.

## 3. ASIC1-mediated $[Ca^{+2}]_i$ increases are unaffected by DOR agonists

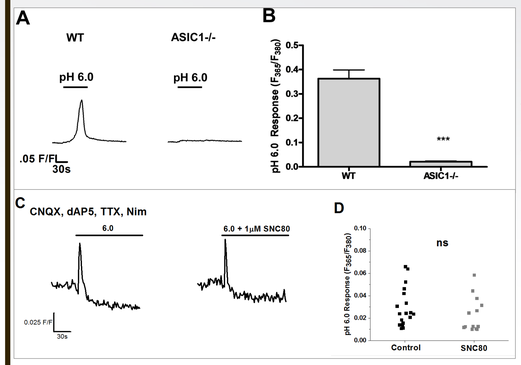



**Figure 3. DOR activation has no statistical effect on ASIC1-mediated $[Ca^{+2}]_i$ increase in hippocampal neurons. (A,B)** ASIC1 is necessary for an acid-induced Calcium signal. $p<0.001$ **(C,D)** SNC80 does not change the neuronal acid-induced Calcium signal.

## Conclusions

1. ASIC-mediated neurotoxicity can be prevented by delta opioid receptor activation through protein kinase-C.
2. DOR-mediated neuroprotection dissociates ASIC activity from acidotoxicity through a novel mechanism.
3. DOR activation may be an inherent protective system to specifically target ASIC1a pathological activity and spare ASIC's physiologic role.

## Future Directions

- Determine the mechanism for DOR modulation of ASIC1.
  - Channel phosphorylation?
  - Accessory proteins?
  - Calcium handling?